REMARKS

I. Formal Matters

Claims 3 and 4 are pending in the application and have been newly rejected.

The Office Action was issued in response to the Appeal Brief filed on March 11, 2002. In view of the arguments made in the Appeal Brief, the Examiner has withdrawn the finality of the Office Action dated June 12, 2001, and withdrawn the rejections of claims 3 and 4 over Miyamoto et al.

II. Claim Rejections Under 35 U.S.C. § 112

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner stated that it is unclear what is intended by the word "derivative" in claims 3 and 4 and suggested deleting the term. The Examiner also asserted that there is insufficient antecedent basis for this limitation in the claim.

Claims 3 and 4 have been amended to delete the word "derivative" and to substitute therefore the word "compound." Accordingly, the rejection is overcome and removal thereof is respectfully requested.

III. Claim Rejections Under 35 U.S.C. § 103

A. Claim 3

Claim 3 was newly rejected under 35 U.S.C. §103 as allegedly unpatentable over *DeLuca* et al U.S. Patent 5,945,410 (US '410) and U.S. Patent 6,306,844 B1 (US '844). According to the Examiner, both references teach 2-methyl and 2-alkyl 19-nor 20(S) vitamin D_3 compounds. The Examiner further asserted that US '410 teaches 1α, 25-dihydroxy-2α and 1α, 25-dihydroxy-2β methyl 19-nor vitamin D_3 (compound 12 and 13, example 1) and the biological activity of 2-

methyl substituted 19-nor 1, 25-$(OH)_2D_3$ compounds and their 20-S isomers. The Examiner specifically referred to lines 36-67, in col. 15 and lines 1-37 in col. 16, where 2-methyl substitutions are said to produce surprisingly potent compounds.

The cited US '844 patent is a CIP of U.S. Patent 6,127,559 (US '559).

The US '844 patent has a publication date of October 23, 2001, and a filing date of July 14, 2000, both of which are after Applicants' actual U.S. filing date of December 29, 1998. Similarly, the US '559 patent has a publication date of October 3, 2000, and a filing date of August 17, 1998, both of which are after Applicants' April 30, 1998, PCT filing date.

Therefore, only the disclosure of the US '410 patent can be relied upon by the Examiner. In order to overcome this rejection, applicants submit herewith two declarations under 37 C.F.R. § 1.131, establishing that the present inventors actually reduced to practice at least two species of the invention prior to the March 17, 1997 filing date of US '410. Therefore, the *DeLuca* references should be removed and the rejection withdrawn.

More specifically, submitted herewith is an unexecuted Rule 131 Declaration by Dr. Toshie Fujishima, one of the inventors. Also submitted as corroboration is an unexecuted Rule 131 Declaration of Dr. Zhaopeng Liu. Executed declarations will be filed when they are received.

In her declaration, Dr. Fujishima explains that prior to March 17, 1997, she synthesized compound (68), (20S)-1α,25-dihydroxy-2β-methyl-3β-vitamin D_3 (Example 2, page 33 of the specification) and compound (72), (20S)-1α,25-dihydroxy-2α-methyl-3β-vitamin D_3 (Example 1, page 32 of the specification). The synthesis of compound (68) is documented in experimental note (1), Exhibit 1, and the synthesis of compound (72) is documented in experimental note (2),

Exhibit 1, both of which are copies of pages from Dr. Fujishima's notebook. The entries on the pages are described in detail in the declaration. Dr. Fujishima also describes NMR spectra of compound (68) (Chart 1, Exhibit 1) and of compound (72) (Chart 2, Exhibit 1) from an analysis that was carried out prior to March 17, 1997. Dr. Fujishima testifies that she reviewed the NMR spectra prior to March 17, 1997 and identified the compounds as those compounds designated as compound (68) and compound (72) in the present application. In addition Dr. Fujishima testifies that the vitamin D receptor affinity of compound (68) and of compound (72) was measured prior to March 17, 1997. (note 3 and Chart 3, Exhibit 1) Further, Dr. Fujishima testifies that she presented the results of the work to her colleagues prior to March 17, 1997. Handouts from the seminar are submitted with the declaration, and are explained in detail by Dr. Fujishima. (Exhibit 2)

The declaration of Dr. Liu corroborates Dr. Fujishima's testimony. Specifically, Dr. Liu states that he remembers that Dr. Fujishima is the author of experimental notes (1), (2), and (3) (Exhibit 1) and that he recalls that Dr. Fujishima planned to present the results of these notes at a workshop. Dr. Liu testifies that to do so, Dr. Fujishima had to submit an abstract, which was due prior to March 17, 1997. (Exhibit 3) Dr. Liu also states that he was present when Dr. Fujishima presented the results of her work on compounds (68) and (72) in a group seminar held prior to March 17, 1997. (Exhibit 2) In his declaration, Dr. Liu describes in detail the handouts from the seminar and states that he understood that Dr. Fujishima had synthesized and confirmed the usefulness of compounds (68) and (72) prior to March 17, 1997. Dr. Liu also states that he understood that Dr. Fujishima had determined a detailed scheme for how to make compounds (68) and (72) prior to March 17, 1997.

In view of the Fujishima and Liu declarations, applicants respectfully submit that two species within the claimed invention had been actually reduced to practice prior to the March 17, 1997 filing date of US '410. Accordingly, applicants have antedated US '410.

B. Claim 4

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over *Trost M. Barry et al* for the reasons of record.

The Examiner's position was that *Trost* discloses a palladium-catalyzed alkylative cyclization of enynes for the synthesis of vitamin D derivatives. The Examiner asserted that the difference between the claimed invention and the disclosure of Trost is that in the present invention a different starting material is used wherein the starting compound of the claimed invention has a methyl group at the 4-position of the compound of formula III and Trost discloses an unsubstituted 4-position, but that both are enynes of formula III. Thus, the Examiner concluded that one of ordinary skill in the art would have been motivated to use the process of *Trost* in order to obtain the instant derivatives since the starting materials would be expected to react similarly.

Applicants respectfully submit that the Examiner has not made a *prima facie* showing of obviousness. To establish a *prima facie* case of obviousness there must be (1) some suggestion or motivation within the reference or in the knowledge generally available to one of ordinary skill in the art to modify the reference; (2) a reasonable expectation of success; and (3) the reference relied upon by the Examiner must teach or suggest all of the claimed limitations. *See Hodesh v. Block Drug Co*, 786 F.2d 1136, 1153, n.5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986);

In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 1438 (Fed. Cir. 1991); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

In this case, there is no teaching or suggestion within the reference to modify the disclosed process such that one of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed 20(S) vitamin D_3 derivatives, having unexpectedly superior properties as shown in the specification on page 39 and in the Declarations under 37 C.F.R. § 1.132 submitted December 30, 1999, (the executed declaration was filed on August 1, 2000) and on November 13, 2001. Applicants submit that it has been established that where a method for preparing purified isomers of compounds, such as the claimed 20(S) vitamin D_3 derivatives, is not taught or suggested by a reference, a *prima facie* case of obviousness has not been established. Applicants rely on the holding *of Emory University v. Glaxo Wellcome, Inc.* (44 USPQ2d 1407 (DC NGa 1997)) citing *In re Hoeksema* (158 USPQ 596, (CCPA 1968)) for the holding that "if the prior art of record fails to disclose or render obvious a method for making a claimed compound at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public."

In addition, Applicants submit that the Examiner failed to consider the claimed invention as a whole. The reference does not teach all of the limitations of the claimed invention, namely, the specifically recited 20(S) form vitamin D_3 derivative compounds. The fact that the reference may teach a similar process is not sufficient by itself to establish obviousness under the fact instensive inquiry required by 35 U.S.C. § 103. *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995)(where the Court reversed the Board of Appeals and the Examiner stating that both had used incorrect methodology in determining obviousness of a process for making a

compound based upon a "general obviousness rule that a claim is obvious if prior art references disclose the same general process using similar starting materials" and stating that no such *per se* rule exists).

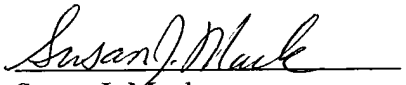
As in the case of *In re Ochiai*, the Examiner's rejection is based upon a general rule of obviousness that a process claim is obvious if the prior art references disclose the same general process using similar starting materials. The Examiner has maintained the position that the starting materials of the claimed invention are analogous to those taught by *Trost et al* because they are both enynes of formula III. As a basis for the rejection the Examiner states and maintains, "[i]t has been held that application of an old process to a[n] analogous material to obtain a result consistent with the teachings of the art would have been obvious to one having ordinary skill." However such an analysis does not take into consideration the fact that the compounds of formula III of the claimed invention are different as well as the fact that the recited 20(S) vitamin D_3 derivative compounds are different and have been shown to possess unexpectedly superior properties over the closest specifically disclosed compounds.

Further, the compound of claim 4 is an intermediate compound rather than a starting material, as incorrectly stated by the Examiner, and the intermediate compound is essential for the claimed process with respect to the preparation of the specific 20(S) form vitamin D recited in the claims. Applicants submit that the data showing unexpectedly superior results of the final product is sufficient to establish the patentability of the claimed process.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

Claim 3 (Amended). A 1,25-dihydroxy-2-methylvitamin D_3 ~~derivative~~compound, wherein the ~~derivative~~compound is

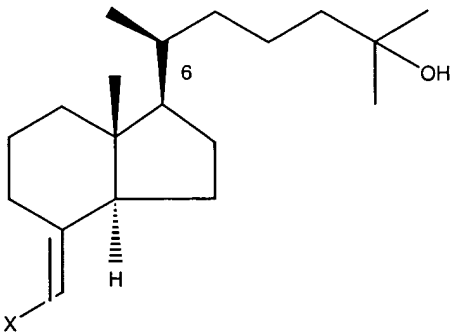
(i) (20S)-1α, 25-dihydroxy-2β-methyl-3β-vitamin D_3;

(ii) (20S)-1 β, 25-dihydroxy-2β-methyl-3α -vitamin D_3;

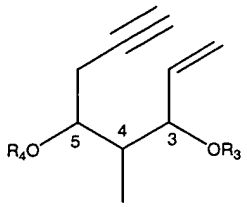
(iii) (20S)-1α, 25-dihydroxy-2α -methyl-3β-vitamin D_3;

(iv) (20S)-1α, 25-dihydroxy-2α -methyl-3α -vitamin D_3.

Claim 4 (Amended) A method for producing a vitamin D_3 ~~derivative~~compound described in claim 3, comprising reacting an exo-methylene compound of formula (II):



wherein X is a bromine atom or an iodine atom, with an ~~ene-yne~~eneyne compound of formula (III):



wherein R3 and R4 are each independently a hydrogen atom or a tri (C_1 to C_7 hydrocarbon) silyl) group in the presence of a palladium catalyst, and optionally removing the protecting group of the tri (C_1 to C_7 hydrocarbon) silyl) group, and further wherein the vitamin D_3 derivative is

(i) (20S)-1α, 25-dihydroxy-2β-methyl-3β-vitamin D_3;

(ii) (20S)-1β, 25-dihydroxy-2β-methyl-3α-vitamin D_3;

(iii) (20S)-1α, 25-dihydroxy-2α-methyl-3β-vitamin D_3;

(iv) (20S)-1α, 25-dihydroxy-2α-methyl-3α-vitamin D_3.